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* NEW YORK STATE BAR ADMISSION PENDING

August 6, 2004

Ms. Kim Nguyen,
Patent Agent
OSI Pharmaceuticals, Inc.
Suite 110
58 South Service Rd.
Melville, NY 11747

Re: Arlindo L. Castelhano et al., Compounds Specific to Adenosine A_3 Receptor and Uses Thereof, U.S. Serial 09/728,616, filed December 1, 2000, claiming the benefit of U.S. Provisional Application No. 60/169,036, filed December 2, 1999 - Our Docket 60390-G

Dear Kim:

Further to our May 7, 2004 letter, we enclose a copy of an Office Action issued July 28, 2004 by the U.S. Patent and Trademark Office in connection with the above-identified application. The enclosed Office Action provides a period of three (3) months for filing a response. Therefore, a response to the February 11, 2004 Office Action is due **October 28, 2004**. However, an extension of time of up to three (3) additional months, i.e. until January 28, 2005 may be obtained upon the payment of a fee.

You should note, however, that since this application was filed after May 28, 2000, it is subject to the patent term adjustment provisions of 37 C.F.R. §§ 1.702-1.705, and therefore the taking of an extension of time may affect any patent term adjustment (extension) that a patent which issues from the subject application might otherwise be entitled to.

Under 37 C.F.R §1.56, persons involved in applying for patents, including inventors, have a duty to disclose all information known to them to be material to the patentability of the invention for which patent protection is being sought. This duty continues throughout the prosecution process and any additional material information of which they became aware should be submitted to the Patent Office. Accordingly, if you know of any material information which should be disclosed to the Patent Office pursuant to 37 C.F.R. §1.56, please advise us.

We look forward to receiving your comments and suggestions for responding to the enclosed Office Action. In the absence of contrary instructions, we intend to prepare and circulate a draft response shortly prior to October 28, 2004.

Please contact John White or me if you have any questions, comments or special instructions.

Sincerely,

Gary J. Gershik

JPW/GJG/MML:wb
Enclosure

cc: John P. White, Esq. (w/o enclosure)

60570-6

OIPE JC73
AUG 0 9 2004
PATENT & TRADEMARK OFFICE

Office Action Summary

Application No.	Applicant(s)	
09/728,616	CASTELHANO ET AL.	
Examiner	**Art Unit**	
Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

JUL 30

Status

1)☒ Responsive to communication(s) filed on *18 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-110,114-124,128-131 and 133-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *76-98* is/are allowed.

6)☒ Claim(s) *99,103-109,117,118 and 133-135* is/are rejected.

7)☒ Claim(s) *100-102,110, 114-116,119-124 and 128-131* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

3mo: 10/28/04
4mo: 11/28/04
5mo: 12/28/04
6mo: 1/28/05 MPL

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed May 18, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 76, 123, 124, and 133 have been amended.

Claims 126 and 127 have been canceled.

Remarks drawn to rejections of Office Action mailed February 11, 2004 include:

Claim objections: which have been overcome by applicant's amendments and have been withdrawn.

Double Patenting Rejections: which have been overcome in part and withdrawn in part.

112 2nd paragraph rejections: which have been overcome by applicant's amendments and have been withdrawn.

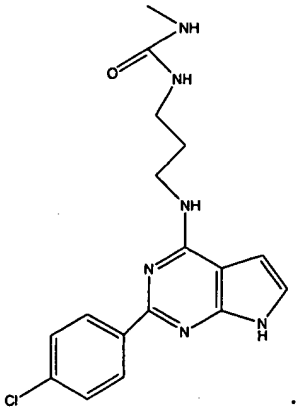
102(a) rejection: which has been overcome by applicant's amendments and has been withdrawn.

An action on the merits of claims 76-110, 114-124, 128-131, and 133-135 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Double Patenting

The rejection of claim 76 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 10 of U.S. Patent No. 6,686,366 is withdrawn as applicants have amended the claims of the instant application to carve out the overlapping structures.

The rejection of claim 99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 4-6 U.S. Patent No. 6,686,366 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the Markush groups of both claim sets comprise a compound of the same structure. Claim 99 comprises a compound having the following structure:



Claims 1 and 4-6 of the '366 patent claim the identical compound wherein the variables of '366 are defined as: m=1 (in claim 6); R_1 (of claim 6) is aminomethyl; R_3 is substituted aryl (chlorine substituted on benzene); and R_5 and R_6 are H.

Applicant's arguments filed May 18, 2004 have been fully considered but they are not persuasive. Applicants argue that the compounds of the instant application are improvements of the previously filed application, and thus are patentable over the prior art Markush group. The examiner notes that the '366 patent is drawn to the identical compound as set forth in claim 99 of the instant application. Moreover, arguments that the instantly claimed compounds are "later filed improvements" are not sufficient to overcome the instant rejection. Absent of a proof to the contrary, clearly setting forth the "improvements" of the compound as set forth in the instant application, the rejection is maintained as proper.

The rejection of claims 124, and 126-131 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-29 of U.S. Patent No. 6,686,366 is withdrawn due to applicant's canceling claims 126-127 and amending claim 76 (from which 124 depends) to carve out the compounds of the prior art.

The rejection of claims 133-135 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-46 of U.S. Patent No. 6,686,366 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to methods of preparing the same class of compounds with identical methodological steps and identical reactants. It is noted that the chemical process that is occurring is an expected reaction based upon the prior art. The use of a novel and unobvious starting material, or a novel and unobvious final product, does

not render an obvious, predictable process patentable. In a chemical process, all of the evidence must be considered on the subject matter as a whole from the viewpoint of one skilled in the art, in the determination of obviousness, and not simply to the patentability of one of the starting materials or final products in the process. The process is deemed obvious to one of ordinary skill in t the art in view of the '366 patent since it involves a predictable and expected reaction, namely, the same reaction steps as the prior arts patent. See ***In re Durden, 763 F.2d 1405, 226 USPQ 359 (Fed Cir 1985).***

The rejection of claim 76 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7 and 8 of U.S. Patent No. 6,680,322 is withdrawn as applicants have amended claim 76 to carve out the compounds of the '322 patent.

The rejection of claims 124, 127, and 129-131 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-33 of U.S. Patent No. 6,680,322 is withdrawn due to applicant's canceling claims 126-127 and amending claim 76 (from which 124 depends) to carve out the compounds of the prior art.

The rejection of claim 133 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 36 of U.S. Patent No. 6,680,322 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to methods of preparing the same class of compounds with identical methodological steps and identical reactants. It is noted that

the chemical process that is occurring is an expected reaction based upon the prior art. The use of a novel and unobvious starting material, or a novel and unobvious final product, does not render an obvious, predictable process patentable. In a chemical process, all of the evidence must be considered on the subject matter as a whole from the viewpoint of one skilled in the art, in the determination of obviousness, and not simply to the patentability of one of the starting materials or final products in the process. The process is deemed obvious to one of ordinary skill in t the art in view of the '366 patent since it involves a predictable and expected reaction, namely, the same reaction steps as the prior arts patent. See ***In re Durden, 763 F.2d 1405, 226 USPQ 359 (Fed Cir 1985).***

It is noted that a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 103-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims are drawn to prodrugs of the compounds of claim 76 or 99 wherein the prodrug is metabolized *in vivo* by a human subject to an active drug which selectively inhibits the A3 adenosine receptor wherein the prodrug is various esters, acetal groups, ketal groups, N-Mannich bases, imines, Schiff bases, oximes, acetals, enol esters, oxazolidines, or thiazolidines.

The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The breadth of the claims includes all of the hundreds of thousands of prodrugs of the formula of claim 76 and 99 as well as the presently unknown list potential prodrug derivatives embraced by claim 103.

The state of the prior art

Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

The level of one of ordinary skill

Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

The level of predictability in the art

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written.

The existence of working examples

There is no working example of any prodrug of a compound of claim 76 or 99.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any composition produced by the method of claim 4 to prevent the development of cancer without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Thus, undue experimentation will be required to determine if any particular compound is, in fact, a prodrug.

Claims 117 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the actual condition which is being treated. The claim is drawn to treating "diseases associated with an A3 adenosine receptor" which is "associated with mast cell degradation". The examiner is unclear as to exactly what is intended to be treated in the instantly set forth claim.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Conclusion

Claims 76-98 are allowed.

Claims 100-102, 110, 114-116, 119-124 and 128-131 are objected to as being dependent upon a rejected base claim.

A shortened statutory period for reply to this action is set to expire THREE MONTHS from the mailing date of this action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
July 15, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

BRUCK KIFLE, PH.D.
PRIMARY EXAMINER

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 60390-G/JPW/GJG/JBC	Serial No. 09/728,616
	INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants: Arlindo L. Castelhano, et al.	
		Filing Date December 1, 2000	Group 1623

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

(b)		Kiichiro, K. et al. "Synthesis of pyrazinecarboxylic acid derivs. - (II) derivs. of 3-aminopyrazinecarboxylic acid" (1961) Yakugaku Zasshi 81: 1650-1653 (Abstract only) **(Exhibit 46);**

EXAMINER	DATE CONSIDERED 7/15/2004

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 60390-G/JPW/GJG/JBC	Serial No. 09/728,616
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants: Arlindo L. Castelhano, et al.	
	Filing Date December 1, 2000	Group 1623

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
		20 02 00 28 7 8 2	3/7/02	Castelhano et al.			
		20 02 00 58 6 6 7	5/16/02	Castelhano et al.			
		20 03 00 36 5 4 5	2/20/03	Castelhano et al.			
		20 03 00 45 5 3 6	3/6/03	Castelhano et al.			
		20 03 00 73 7 0 8	4/17/03	Castelhano et al.			

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	WO	9 5 1 9 7 7 4	7/27/95	PCT (Exhibit 1).				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER _____ DATE CONSIDERED 7/15/2004

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited	Application/Control No. 09/728,616	Applicant(s)/Patent Under Reexamination CASTELHANO ET AL.	
	Examiner Traviss C McIntosh	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,686,366	02-2004	Castelhano et al.	514/264.1
*	B	US-6,680,322	01-2004	Castelhano et al.	514/252.02
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Wolff et al., "Burger's Medicinal Chemistry, 5th edition, vol. 1", John Wiley & Sons, 1995, pp. 975-977.
	V	Banker et al., "Modern Pharmaceutics, 3rd edition", Marcel Dekker, NY, 1996, pp. 596.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume I: Principles and Practice

Edited by

Manfred E. Wolff

ImmunoPharmaceutics, Inc.
San Diego, California

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use of liver microsome preparations as shown for new dopaminergic compounds (245), and to include human microsomes in order to gain some insight into the situation potentially encountered in humans.

8.6 Validity of Classical Pharmacokinetic Concepts for Prodrug Design

As seen in the previous paragraphs, classical pharmacokinetic concepts can be used for the study of prodrugs despite the fact that they have essentially been derived from theoretical considerations related to the situation where the parent compound is the active moiety. As for metabolite kinetics, difficulties arise when the prodrug is not totally biotransformed to the "drug." There is one situation, however, in which it is questionable whether these concepts are fully appropriate, namely drug targeting. For example, if a prodrug is very specifically targeted to one type of cells or to one organ system, it might be necessary to define a "targeting index" to describe distribution of the prodrug and the active moiety, since a concept such as the apparent volume of distribution might only poorly describe the distribution properties of the therapeutic agent. The same restriction may apply to the concepts of systemic availability, systemic clearance and apparent half-life of elimination. This does not mean that classical pharmacokinetic concepts would become invalid because they are robust and well validated, but that some creativity is probably necessary in order to improve the descriptive power of pharmacokinetics in order to allow comparisons of "drug" and prodrug or between prodrugs. Similar considerations also apply to the concepts basic to biopharmaceutic evaluations. If the necessity to define new pharmacokinetic parameters for the description of targeted prodrugs is accepted, it will be of utmost importance to define only concepts that can be quantified based on experimental data. It is possible that development of imaging techniques such as PET- or NMR-scan will give an impetus to these foreseeable developments in pharmacokinetics.

A problem requiring special attention is the stereoselective *in vivo* activation of prodrugs derived from racemic mixtures, as exemplified by the stereoselective hydrolysis of *O*-acetyl-propanolol (246), for which it was also found that the selectivity of plasma enzyme urase differs from that of liver and intestine enzymes.

9 SOME CONSIDERATIONS FOR PRODRUG DESIGN

9.1 Rationale of Prodrug Design

The design of prodrugs in a rational manner requires, as stated by Bundgaard (9), that the underlying causes which necessitate or stimulate the use of the prodrug approach be defined and clearly understood. It may then be possible to identify the means by which the difficulties can be overcome. The rational design of the prodrug can thus be divided into three basic steps:

- Identification of the drug delivery problem.
- Identification of the physicochemical properties required for optimal delivery.
- Selection of a prodrug derivative that has the proper physicochemical properties and that will be cleaved in the desired biological compartment.

In this context it must be accepted that a very close collaboration is needed between the pharmaceutical chemists active in drug synthesis and those working in the area of xenobiotic metabolism. This is particularly important if more targeted prodrugs are designed in function of enzymes available at the right place, in the right amount and with the right prodrug specificity.

9.2 Practical Considerations

In the rational design and synthesis of prodrugs, several factors should be considered before starting the development of a new compound intended for large-scale production (247):

- The chemical intermediates or modifiers should be available in a high state of purity at reasonable cost.
- Complicated synthetic schemes should be avoided and purification steps should be efficient without markedly increasing production costs. The production should be easy to scale-up from the bench mark to industrial production.
- The prodrug should be stable in bulk form. This is of particular importance for substances like esters, which are likely to be degraded in the presence of even trace amounts of moisture.
- The *in vivo* lability should be efficient to permit release of the active moiety at a rate adequate to ensure its therapeutic activity. Regeneration can be either chemical (pH effects) and/or enzymatic.
- The prodrug and the "carrier moiety" should be nontoxic. Relatively "safe" moieties include amino acids, short to medium length alkyl esters, and some of the macromolecules described previously.
- The pharmacokinetics of the active moiety should be well documented before starting prodrug synthesis, and, at a later stage, prodrug kinetics should be thoroughly investigated in man.
- The biopharmaceutical consequences for prodrug formulations should be carefully evaluated.
- Last but not least, the prodrug should present some clinically relevant advantages over the active principle administered directly. In this context, it must be remembered that modification of one pharmacokinetic property frequently alters other properties of the drug molecule and caution must thus be exercised when embarking on a program of this nature.

10 CONCLUSIONS

Although prodrug design started more than 30 years ago and many reviews have been written on this subject, very little information is available in official guidelines or pharmacokinetic textbooks on the regulatory requirements or data analysis for this type of compounds. This chapter is an attempt to gather and confront available information on the subject.

Some basic problems have, however, been left untouched. For example, the difficulty of extrapolating data from animal to humans encountered during toxicokinetic and toxicologic studies with drugs is amplified with prodrugs since not only metabolism of the active moiety might differ, but also its availability from the prodrug. As a matter of fact, there is presently no published rationale for the conduct of animal and human pharmacokinetic programs during prodrug research and development.

The authors concluded a review on prodrugs (7), quoting the question asked in 1985 (248) by Stella et al.: "Do prodrugs have advantages in clinical practice?" The opinion was the following: "Today, the answer is certainly YES in some particular cases, but for many drugs this aspect of drug design has received no clear and satisfactory solution. The main reason for this situation is that most prodrugs have been synthesized starting from valuable and well-known drugs. As a consequence, the potential advantage of the new chemical entity over its "seasoned precursor" has often been only marginal. It is thus important that in the future, drug design of new chemical entities should incorporate

"delivery and/or targeting components" from the earliest stages of research and development. This strategy might help substances too toxic, or unable to show adequate pharmacologic effects in their basal form to go through primary and secondary screening, before successfully reaching human testing. It is evident that if such an approach were to become an integral part of basic drug design and not just a hindsighted attempt to solve problems associated with older drugs, it would also be necessary to develop new biopharmaceutical and pharmacokinetic approaches to tackle the new challenges." After five years, the authors still believe that this is a valid statement.

After this chapter, which focused more on pharmacokinetic aspects than on chemical synthesis, we can conclude that, indeed, additional thinking on new ways to approach the toxicokinetic and the clinical pharmacokinetics of prodrugs and their active moiety is of paramount importance if prodrug design is to remain (or to become?) an important part for research and development of new therapeutic agents. In parallel, great efforts must be undertaken in order to better understand the molecular basis of xenobiotic metabolism. It should then be easier to synthesize compounds which would show the most appropriate physicochemical characteristics.

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B. Prodrugs

A *prodrug* is a compound resulting from chemical modification of a biologically active compound that will liberate the active form in vivo by enzymatic or hydrolytic cleavage. The primary purpose in forming a prodrug is to modify the physicochemical properties of the drug, usually to alter the membrane permeability of the parent compound. This change in physicochemical properties of the drug influences the ultimate localization of the drug. There are various reasons for formulating a prodrug system. If the parent compound is insoluble, this can be modified [62]. If it is easily degraded, modification can protect the parent compound from enzymatic or hydrolytic attack. Modifications can also reduce side effects, such as GI irritation [63]. Several drugs are now marketed in the form of a prodrug; for example, sulindac, a nonsteroidal anti-inflammatory agent, and numerous angiotension-converting enzyme (ACE) inhibitors. The necessary conversion of prodrug to parent can occur by a variety of reactions, the most common being hydrolytic cleavage [64]. The prodrug ester forms of a hydroxyl or carboxyl group of the parent compound can be readily cleaved by blood esterase. Other activation processes may include biochemical reduction or oxidation. However the conversion occurs, to achieve sustained drug action, the rate of conversion from prodrug to active compound should not be too high [65]. Site-specific, controlled delivery is achieved by the antiviral prodrug acyclovir, being converted to active form by a virus-specific enzyme [66]. Sustained release of steroid prodrugs, especially progestagens and progestagen–estrogen combinations, have seen a substantial amount of clinical experience, both as a means of birth control and as symptomatic menopausal treatment [67].

The concept of the double prodrug (proprodrugs), may allow more controlled delivery of various prodrug compounds [68]. For example, if a prodrug that shows site-specific activation, but has poor transport properties or stability problems, it could be converted to a proprodrug that transported better or is more stable (Fig. 12). Prodrug systems have been taken even further by including as prodrugs, polymer prodrugs, in which a drug is covalently linked to a polymer backbone. This type of system could encompass a staggering number of possibilities. Encouraging results have been shown with mitomycin [69,70], for example.

The most serious disadvantage to the prodrug approach to controlled–sustained delivery is that extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and, therefore, requires extensive and costly studies to determine safety and efficacy.

C. Nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm. They can be used as drug carriers, with the drug encapsulated, dissolved, adsorbed, or covalently attached

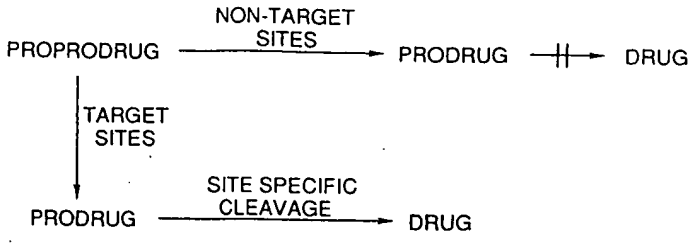

Fig. 12 Illustration of prodrug and proprodrug concept.

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